

REMARKS

Claims 1-30 are pending in the application. Claims 1-30 are rejected under 35 USC § 103(a). Claims 1-30 are also rejected on the ground of nonstatutory obviousness-type double patenting.

Applicants respectfully request reconsideration of the application, withdrawal of all rejections, and allowance of the application in view of the remarks below.

Amendments to the Claims

Without prejudice to the Applicants' rights to present claims of equal scope in a timely filed continuing application, to expedite prosecution and issuance of the application, the Applicants have amended Claims 1-5, 7, 15 and 19 and cancelled Claims 8-14 and 20-30. The amended claims are supported by the specification. See, *e.g.*, Paragraphs [0177], [0252], [0274]-[0276], [0282], [0321], [0322], [0363], [0440], [0505], and [0536].

The amendments to the claims do not introduce new matter. Applicants respectfully submit that the amendments to the claims put the case in condition for allowance. The Examiner is respectfully requested to enter the amendments to the claims and allow all amended claims.

Claim Rejections Under 35 USC § 103

Claims 1-30 are rejected under 35 USC § 103 as being unpatentable over U.S. Patent No. 6,514,482 to Bartus et al. ("Bartus") in view of U.S. Patent No. 6,041,777 to Faithful et al. ("Faithful").

The Office Action states that "Bartus teaches a method of pulmonary delivery of a medicament, which includes administering ... particles ..., wherein the particles preferably have an aerodynamic diameter between about 1 and 5 μm ." Office Action at 2. The Office Action further states that Bartus discloses medicaments containing from 1 to about 90 weight percent of drugs that are delivered via dry powder inhaler, metered dose inhaler, nebulizer or instillation techniques. *Id.* at 2-3.

The Office Action states that Bartus lacks "teachings on producing condensation aerosol and also lacks specific disclosure on the presence of less than 5% degradation products." *Id.* at 3. The Office Action states in summary that Faithfull teaches methods and apparatus for closed-

circuit ventilation therapy, including the use of nebulizers to provide fluorochemicals and/or pharmaceutical agents, heated above body temperature, to a ventilating gas in the form of a vapor and that this is accomplished by spraying or contacting a wetted surface or wick with the gas to form droplets. The Office Action further states that Faithful also discloses that the method provides for the independent delivery of pharmaceutical agents or their use in conjunction with other vapors. *Id.* at 4-5.

The Office Action states that it “would have been obvious to a person of ordinary skill in the art at the time the invention was made to have modified the method of delivering a medicament to a patient’s respiratory tract of Bartus, by adding the steps of heating the composition and having the patient inhale the condensates, because of the disclosed benefits of such a method, including minimized trauma to the lungs and a better resolution of pulmonary and systemic disorders, as taught by Faithful.” *Id.* at 4.

Applicants respectfully disagree in view of the elements of the claims and the disclosures of Bartus and Faithfull. Bartus fails to teach or disclose the claimed article or method; in particular, Bartus does not teach or disclose a heat conductive substrate having a surface or a film comprising a drug composition on the surface. Rather Bartus is directed to a method of delivering low tap density particles for the treatment of CNS disorders and in particular, Parkinson’s disease, via dry power inhalers or metered dose inhalers. Nowhere does Bartus disclose or suggest forming an aerosol by vaporizing the drug composition by heating the substrate and condensing the vaporized drug composition. Dry powder inhalers, metered dose inhalers, nebulizers, or instillation techniques do not vaporize the drug and then form a condensate of the drug. Additionally, in Bartus there is no disclosure of how one would form such an aerosol comprising an antiparkinsonian drug or any other drug to generate an aerosol having 10% or less drug degradation products, or how to obtain aerosols having an MMAD within the range of 0.01 and 3 μm , when vaporizing the drug composition by heating the substrate and condensing the vaporized drug composition. Nor does Bartus disclose the claimed drug compositions and film thickness combinations.

Faithfull does not cure these deficiencies or make obvious in view of Bartus how to accomplish these tasks. Faithfull does not disclose or teach the article or method defined by Applicants’ claims. Faithfull does not teach or disclose a heat conductive substrate having a surface and a film comprising a drug composition on the surface. Rather, Faithfull discloses the

use of a warmed fluorochemical as a solvent for delivering the active compound “oxygen” to the lungs of the patient using a ventilation system. The active or therapeutic compound or drug in Faithfull is not heated to produce a vapor or condensed to form an aerosol. Instead, Faithfull requires the use of a wetted surface or wick to get the fluorochemical (solvent) to form a droplet. Moreover, as stated in the Office Action, the fluorochemical in the Faithfull reference is being delivered to the lung as a vapor and not as an aerosol. See Office Action at 3, lines 19-20 (“As the fluorochemical vapor cools in the body it is deposited on the pulmonary surfaces” (emphasis added)). Faithfull does not disclose how to form an aerosol by vaporizing the drug composition by heating the substrate and condensing the vaporized drug composition. Nor does Faithfull disclose how to generate such an aerosol having 10% or less drug degradation products, or how to obtain an aerosol having an MMAD between 0.01 and 3 μm . Nor does Faithfull disclose the claimed drug compositions and film thickness combinations.

The Office Action suggests that condensates by their nature have a high percentage of purity of the drug and less degradation products. *Id.* at 4. Applicants respectfully disagree. The mere fact that an aerosol is formed by condensation does not mean that the aerosol will have a high percentage of drug and less degradation products.

Faithfull does not cure the deficiencies of Bartus. Accordingly, the Office Action fails to establish a *prima facie* case of obviousness, as each and every element of Applicants’ claimed invention is not taught or disclosed by these references. Moreover, there would be no motivation to combine the references to achieve Applicants’ presently claimed invention. Even if the cited references were combined, the claimed invention would not result because neither Bartus nor Faithfull disclose or teach the elements of the claimed article or method.

In light of the above arguments, Applicants respectfully request withdrawal of the rejection of Claims 1-30 under 35 USC § 103, over Faithfull et al., in view of Bartus et al.

Claims 1-30 are rejected under 35 USC § 103 as being unpatentable over U.S. Patent No. 6,514,482 to Bartus et al. (“Bartus”) in view of U.S. Application Publication No. 20040016427 of Byron et al. (“Byron”).

The Office Action states that Bartus “lacks disclosure on condensation aerosols and the devices for producing condensates involved in the method of therapy,” but that Byron “disclose a

method and apparatus for generating an aerosol ... formed by supplying a material in liquid form to a tube and heating the tube such that the material volatilizes and expands out of an open end of the tube.” *Id.* at 4. The Office Action goes on to state that the volatilized material combines with ambient air such that the volatilized material condenses to form the aerosol and that the aerosols are intended for inhalation and typically have a mass median particle diameter of less than 2 microns. Thus, according to the Office Action, it would have been obvious to take the device of Byron and use it to deliver the aerosolized composition of Bartus to a subject’s respiratory tract as it would be desirable to provide an aerosol delivery article capable of making small particles without exposure to significant heat or high temperatures. *Id.* at 5.

Applicants respectfully disagree. One of skill in the art seeking to prepare and administer aerosolized compositions for delivery to a subject’s respiratory tract without exposure to significant heating or high temperatures would not have to look beyond the disclosure of Bartus. Moreover, Bartus does not teach that small particles are desirable. To the contrary, Bartus states that larger, low density particles aerosolize more efficiently and avoid phagocytic engulfment by alveolar macrophages more effectively than smaller, denser aerosol particles. Bartus, col. 13, lines 61-64.

“The aerodynamic diameter can be calculated to provide for maximum deposition within the lungs. Previously this was achieved by the use of very small particles of less than about five microns in diameter, preferably between about one to about three microns, which are then subject to phagocytosis. Selection of particles which have a larger diameter, but which are sufficiently light (hence the characterization “aerodynamically light”), results in an equivalent delivery to the lungs, but the larger size particles are not phagocytosed. Improved delivery can be obtained by using particles with a rough or uneven surface relative to those with a smooth surface” (Bartus, col. 13, line 65, to col. 14, line 7).

As pointed out in the Office Action, the aerosols generated by the device of Byron typically have a mass median particle diameter of less than 2 microns, while Bartus teaches that the preferred size range of particles is at least about 5 microns, preferably between about 5 microns and 30 microns. See, *e.g.*, Bartus, col. 12, lines 60-66, and col. 14, lines 12-14. Thus, Bartus teaches away from delivering aerosol compositions using the device of Byron.

Moreover, one of skill in the art would not have a reasonable expectation that the device of Byron would successfully form an aerosol suitable for inhalation, particularly one that has the claimed features (e.g., 10% by weight or less drug degradation products; an MMAD between 0.01 and 3 μm ; etc.), from the compositions of Bartus. For instance, under the method of Byron, the compositions of Bartus ("solid component") would have to be put into liquid form by combining with a "liquid component." Byron, Paragraph [0076]. However, Byron fail to provide specific guidelines for selecting an appropriate "liquid component" for a given drug ("solid component") or for predicting what effect heating the mixture will have on the solid component. This is further complicated when the solid component contains one or more additional component in addition to the drug, such as the surfactants, phospholipids, amino acids, etc., taught in Bartus. Bartus, col. 8, line 42, to col. 11, line 53.

Whether taken alone or in combination, neither Bartus nor Byron teach or suggest all of Applicants' claimed elements. Both Byron and Bartus lack specific disclosure of a film comprising a drug composition on the surface of a heat conductive substrate, the claimed drug compositions and film thicknesses combinations, an aerosol having 10% or less drug degradation products, or an MMAD between 0.01 and 3 μm .

Thus, these references singly or in combination do not teach or suggest all of Applicants' claim elements, but rather teach away from the claimed invention. Accordingly, the Office Action fails to establish a *prima facie* case of obviousness. Furthermore, there would be no motivation to combine the references to achieve the presently claimed invention, nor is it seen how the combination of the references would achieve the presently claimed invention.

In light of the above arguments, Applicants respectfully request withdrawal of the rejection of Claims 1-30 under 35 USC § 103, over Byron, in view of Bartus.

Double Patenting

Claims 1-30 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of U.S. Patents (a) 6,776,978, (b) 7078,018 and (c) 6,814,955, as these claims are said to be "either anticipated by, or would have been obvious over, the reference claims." *Id.* at 6.

Claims 1-30 also are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of 72 U.S. Patents and 32 U.S. patent applications

listed in a table that appears on pages 7 and 8 of the Office Action.*

Applicants have reviewed the listed patents and applications and in order to remove the rejection agree to file terminal disclaimers with regard to the patents and applications listed in the corresponding Schedule, once patentable subject matter has been determined. Applicants believe that the above remarks address the Examiner's concerns and respectfully request reconsideration of the application, withdrawal of all rejections, and allowance of the application in view of these actions and remarks.

Conclusion

The Applicants appreciate the Examiner's careful and thorough review of the application and submit that the Examiner's concerns have been addressed by the amendments and remarks above. The Applicants accordingly request the Examiner to withdraw all rejections and allow the application. In the event the Examiner believes a telephonic discussion would expedite allowance or help to resolve outstanding issues relating to the prosecution of the application, then the Examiner is invited to call the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to Deposit Account No. 19-5117, if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to be charged to Deposit Account No. 19-5117.

Respectfully submitted,

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* Applicants note that the following U.S. Patents are listed twice: (a) 6,994,843; (b) 6,783,753; (c) 7,060,254; (d) 7,078,016; and (e) 7,070,765. In addition, Applicants believe that U.S. Patent No. 6,737,046 was inadvertently included in the list as it does not have a common inventor and is not commonly assigned or owned.